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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev. 2/95)

1- File Copy

Office Action Summary	Application No. 08/872,527	Applicant(s) Guo, Y.
	Examiner Thomas Cunningham	Group Art Unit 1644

X Responsive to communication(s) filed on *Aug 14, 1998* .

This action is **FINAL**.

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

X Claim(s) *1-22 and 33-51* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

Claim(s) _____ is/are allowed.

X Claim(s) *1-22 and 33-51* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is approved disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All Some* None of the CERTIFIED copies of the priority documents have been

received.

received in Application No. (Series Code/Serial Number) _____ .

received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- *SEE OFFICE ACTION ON THE FOLLOWING PAGES* ---

1. Claims 1-22 and 33-51 are active. Applicant has previously elected bispecific monoclonal antibodies as a species of bridge molecule. Such a species was indicated as being encompassed by claims 1-22 and 33-48. Applicant further elected the method exemplified in Example 6.6 and Figs 5 and 6. These examples encompass use of CD28:gp55 bispecific monoclonal antibodies.

2. Applicant has confirmed on page 6 of the last response (Paper No.7) that Nature Medicine 4:1-5 (April 1997) does not refer to an article by Guo et al.

3. (Withdrawn) The prior rejection of claims 1-22 and 33-51 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the compositions and methods of Example 6.6, does not reasonably provide enablement for other materially different CD28:gp55 bispecific antibodies, treatment of cancer cells not comprising gp55, treatment of cancer cells not comprising receptors for IFN-gamma or TNF.

Different monoclonal antibodies would be expected to bind to distinct epitopes of CD28 or gp55 and induce functionally distinct responses. For instance, a monoclonal antibody that binds to a portion of CD28 not involved in coactivation would not be expected to coactivate anti-tumor T cells.

Tumor cells which lack the gp55 determinant would not be targeted by antibodies which bind to gp55. Methods of using bispecific antibodies comprising determinants which bind to gp55 would not be expected to target and destroy tumor cells comprising non-gp55 antigens.

Tumor cells that do not express receptors for IFN-gamma or TNF would not be expected to react to the presence of these mediators. Paul indicates that cytokines must bind to specific cellular receptors in order to exert a biological effect.

--Applicant's arguments have been considered and are persuasive with respect to the elected species.

4. Claims 1-22 and 33-51 to the extent that they embrace all the parameters of Example 6.6 are enabled for treatment of mice bearing hepa 1-6 tumor cells. Applicant has defined the elected species in accordance with the parameters of Example 6.6.

5. Claims 1-22 and 33-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over admissions in the specification, Li et al., J. Immunol. 153:421 (1994), Renner et al., Science 264:833 (1994) or Krummel et al., J. Exp. Med. 182:459-465 (1995), in view of Paul, Fundamental Immunology (1993) and Darlington et al., JNCL 64:809 (1980).

The claims are directed to products and methods of using products such as bispecific monoclonal antibodies (Bi-MAbs) comprising a determinant that binds to CD28 and a determinant that binds to a tumor-associated antigen such as gp55.

The specification admits that it was known how to make bispecific antibodies, see e.g. page 33, lines 4-7.

McGowan et al. teach that stimulation of T cells via ligands that bind to CD28 on T cells induce cell-mediated responses that amplify both CD4+ and CD8+ T cell responses, see abstract.

Renner et al. teach that bispecific monoclonal antibodies to bind to tumor-associated antigens (CD30) and to either CD3 or CD28 "target human T cells to the tumor cells in vivo". Page 833 teaches preactivation of T cells using interleukin 2 and antibody to CD3.

Krummel et al. teach that antibody engagement of CD28 on T cells augments T cell responses and can supply costimulation to T cells encountering APCs deficient in costimulation (Hepa 1-6 cells are deficient in antigen presentation because they lack MHC Class I expression, see pages 29-30 of the specification).

Paul, Fundamental Immunology teaches the activities of IFN-gamma and TNF.

The primary references do not teach antigens, like gp55, from hepatoma cells such as HePa 1-6.

Darlington et al. teach hepatoma cells, see also page 29 of the specification.

It would have been prima facie obvious to one of ordinary skill in the art at the time of invention to make bispecific antibodies comprising determinants that bind to CD28 on T cells and determinants that bind to antigens on tumor cells, such as gp55 on HePa 1-6 cells for the purpose of targeting T cells to hepatoma cells via a bridging antibody, that would bind to both T cells and tumor cells. Further, based on the teachings of the primary references one with ordinary skill in the art would have expected that such bispecific antibodies would provide costimulation to CTLs and thus enhance antitumor CTL activity. The addition of IFN-gamma and TNF would be expected to provide activation of antigen presenting cells like macrophages, augment T cell responses and other cellular responses such as increases in neutrophil adhesion useful for targeting or destroying tumor cells.

While the cited art may not teach the specific hepatoma antigen, gp55, there does not appear to be anything unique about this antigen to distinguish it from hepatoma antigens in general. The critical characteristic of hepatoma antigens is that they are expressed as targets by hepatoma cells to permit binding of an CD28 specific product.

--Applicant's arguments on pages 13-18 of the last response have been considered, but are not persuasive. The concept of targeting tumor cells using bispecific antibodies that bind to both T

cells and tumor cells was well known in the prior art as is evidenced by Renner et al. who clearly teach the benefits of using bispecific antibodies to target T cells via costimulatory molecules like CD28 to tumor cells. The benefits of targeting T cells by antibody binding to costimulatory ligands like CD28 are taught by references like McGowan et al. Motivation for use of IFN-gamma and TNF to promote antigen presentation and further activate T cells is evidenced by Paul.

--Applicant is encouraged to contact the Examiner to discuss whether compositions useful for active immunization distinguish over the cited prior art. See for instance claim 1, step (a) which involves active immunization with a diseased cell.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas M. Cunningham, Ph.D., J.D., whose telephone number is (703) 308-3968. Dr. Cunningham can generally be reached Monday through Thursday from 7:30AM to 6:00 PM. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC

THOMAS M. CUNNINGHAM
PRIMARY EXAMINER
GROUP 1800